APPENDIX A

DECLARATION UNDER 37 C.F.R. § 1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

	Atty. Docket No.:	**019870.052201**	**PATENT**
Application of:	Lin et al.	Examiner:	Blessing M. Fubara
Serial No.: Filed:	10/645,744 August 20, 2003	Group Art Unit:	1618
Entitled:	COMPOSITION FOR THE CARRYING AND DELIVERY OF BONE GROWTH INDUCING MATERIAL AND METHODS FOR PRODUCING AND APPLYING THE COMPOSITION	Conf. No.:	9151

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DECLARATION OF DR. STEVE T. LIN PURSUANT TO 37 C.F.R. § 1.132

I, Dr. Steve T. Lin declare that:

1. I am one of the inventors of the invention in U.S. Patent Application No. 10/645,744 filed on August 20, 2003, and titled "Composition for the Carrying and Delivery of Bone Growth Inducing Material and Methods for Producing and Applying the Composition".

BACKGROUND

2. I attended University of Chinese Culture, Taiwan, from 1965-1971, from which I received a Bachelor of Science degree in Chemical Engineering.

3. I attended South Dakota School of Mines & Technology, Rapid City, SD, from 1972-1973 from which I received a Master of Science degree in Chemical Engineering.

4. I attended Drexel University, Philadelphia, PA, from 1974-1976 from which I received a Master of Science degree in Biomedical Engineering.

5. I attended Washington University, St. Louis, MO, from 1976-1981 from which I received a Doctor of Science degree in Biomedical Engineering.

6. I was a Research Specialist at Hexcel Corporation in Dublin, CA from 1981 to 1984.

7. I was the Manager of Advanced Technology at Orthomatrix Incorporated in Dublin, CA from 1984 to 1986.

8. I was employed by Bristol-Myers Squibb, Zimmer, Inc. in Warsaw, IN from 1986 to 1999, where I held many positions including Senior Director of Biomaterial Science and Implant Technology.

9. Since 1999 I have been employed by Exactech, Inc. in Gainesville, FL, where I currently hold the position of Vice President, Biologics R/D and Chief Technology Officer.

10. A complete curriculum vitae is enclosed as Exhibit A.

11. I have read the Final Office Action mailed on February 23, 2009 from the United States Patent and Trademark Office and am submitting this Declaration to respond to the Examiner's comments in the Final Office Action mailed on February 23, 2009 from the United States Patent and Trademark Office.

THE FEBRUARY 23, 2009 FINAL OFFICE ACTION

12. I understand that the Examiner has rejected claims 1, 2, 5-11, 13, 16, 18, 19, 24, 27, 28, 31-37, 39, 43, 45, 46, 51 and 104-107 under 35 U.S.C. 103(a) as being unpatentable over Jarrett et al. (WO 98/12243) in view of Helm et al. ("Utilization of type I collagen gel, demineralized bone matrix, and bone morphogenetic protein-2 to enhance autologous bone lumber spinal fusion," in J Neurosurg 86: 93-100, 1997) or Bolander et al. ("The use of Demineralized Bone Matrix in the Repair of Segmental Defects," in the Journal of Bone and Joint Surgery, 1986, 1264-1274).

13. I also understand that the Examiner has rejected claims 1, 2, 4-11, 13, 16, 18, 19, 24, 27, 28, 30-37, 39, 43, 45, 46, 51 and 104-107 under 35 U.S.C. 103(a) as being unpatentable over Jarrett et al. (WO 98/12243) in view of Helm et al. ("Utilization of type I collagen gel, demineralized bone matrix, and bone morphogenetic protein-2 to enhance autologous bone lumber spinal fusion," in J Neurosurg 86: 93-100, 1997) or Bolander et al. ("The use of Demineralized Bone Matrix in the Repair of Segmental Defects," in the Journal of Bone and Joint Surgery, 1986, 1264-1274) and further in view of Maddox et al. ("Optimizing Human Demineralized Bone Matrix for Clinical Application," in Tissue Engineering, Vol. 6, No. 4, 2000, pages 441-448).

THE JARRETT ET AL. (WO 98/12243) REFERENCE

14. I have read the Jarrett et al. reference in detail. As the abstract states, Jarrett et al. discloses water-soluble macromers including at least one hydrolysable linkage formed from carbonate or dioxanone groups, at least one water-soluble polymeric block, and at least one polymerizable group, and methods of preparation and use thereof. The macromers can be used to encapsulate cells, deliver prophylactic, therapeutic or diagnostic

agents in a controlled manner, plug leaks in tissue, prevent adhesion formation after surgical procedures, temporarily protect or separate tissue surfaces, and adhere or seal tissues together.

15. The Examiner first cites to Jarrett et al. at page 25, lines 11 and 12, for support for use of the Jarrett et al. carrier composition in orthopedic surgery, as bone repair. I have reviewed the referenced page and note that the cited material is written in the sub-section entitled "Sealing Leaks in Tissue" which is part of the general section entitled "Application for the Macromers. Method of Treatment". The general section states that "[g]enerally, any medical condition which requires a coating or sealing layer may be treated by the methods described herein to produce a coating with better adherence"; and the sub-section states that "[i]n orthopedic surgery, uses include tendon repair, bone repair, including filling of defects, and meniscus repair".

16. It is my opinion that the sections described above would lead a person of ordinary skill in the art to consider using a Jarrett et al. carrier composition for sealing a leak in a bone, e.g., for repairing a bone defect with a leak such as a cerebrospinal fluid (CSF) leak. A CSF leak may occur from the nose, from the external auditory canal, or from a traumatic or operative defect in the skull or spine. The fluid leak is a result of meningeal dural and arachnoid laceration with fistula formation. In fact, the examples found in Jarrett et al. support this teaching of using a Jarrett et al. carrier composition for sealing a leak in a bone. Example 5, at pages 41-42 of Jarrett et al., describe "Sealing of Dural Leak in Canine Craniotomy".

17. The Examiner then cites to Jarrett et al. at page 27, line 2 to page 28, line 13, for support for use of the Jarrett et al. carrier composition as a drug delivery device for the delivery of therapeutic agents. I have reviewed the referenced pages and note that the cited material is written in the section entitled "Controlled delivery of incorporated agents". This section states that "[a]nother preferred application involves locally applying an incorporated agent, such as a prophylactic, therapeutic or diagnostic agent, to tissue surfaces of a patient. The method includes the steps of mixing an agent to be incorporated with an aqueous solution including a suitable polymerization initiator, such as a light-sensitive free-radical polymerization initiator, and a macromer, to form a coating mixture. Tissue surfaces are coated with the coating mixture and the macromer is polymerized, for example, by exposure of the coating mixture to an effective amount of light of an appropriate wavelength."

18. Consequently, it is my opinion that this totally unrelated section described at pages 27-28 of Jarrett et al., would lead a person of ordinary skill in the art to consider using a Jarrett et al. carrier composition for the controlled delivery of an agent to a tissue surface to treat a localized medical condition.

19. Therefore, I disagree with the Examiner combining the teachings of the section entitled "Application for the Macromers. Method of Treatment" at pages 24-26 of Jarrett et al., with the teachings of another totally unrelated section entitled "Controlled delivery of incorporated agents" at pages 27-28 of Jarrett et al., to come up

with the claimed invention because sealing a leak in a bone is not related to controlled delivery of an agent to a tissue surface to treat a localized medical condition. Consequently, a person of ordinary skill in the art reading Jarrett et al., including the totally unrelated passages cited above, would not have been motivated to consider using a Jarrett et al. carrier composition comprising osteotherapeutic material(s) to promote the formation of new bone.

THE EXAMINER'S COMBINATION OF THE SECONDARY REFERENCES

20. The Examiner states at page 5 of the Final Office Action mailed on February 23, 2009 from the United States Patent and Trademark Office that "[w]hile Jarret discloses the carrier composition of the claimed invention, and while Jarret discloses that the carrier composition is a drug delivery device and specifically mentions the use of the composition for repair of bone, the carrier composition of Jarret does not contain demineralized bone matrix material. However, it is known in the art that deminarlized bone matrix is used for bone repair according to Helm and Bolander. Therefore, taking the general teachings of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that inclusion of demineralized bone matrix in the composition of Jarret would effectively repair bone." I respectfully disagree for at least the following reasons:

21. Several categories of bone graft substitutes exist and encompass a variety of materials, material sources, and origins (natural vs synthetic). Many are formed from composites of 1 or more types of material. Laurencin et al. have suggested a classification scheme of material-based groups:

- Allograft-based bone graft substitutes involve allograft bone, used alone or in combination with other materials. Bound within the extracellular matrix of bone tissue are the full cocktail of bone growth factors, proteins, and other bioactive materials necessary for osteoinduction and, ultimately, successful bone healing. To capitalize on this cocktail of proteins, the desired factors and proteins must be carefully preserved while the mineral components are removed using a demineralizing agent such as hydrochloric acid. The mineral content of the bone is degraded, and the osteoinductive agents remain in a demineralized bone matrix (DBM).
- Factor-based bone graft substitutes are natural and recombinant growth factors such as transforming growth factor-beta (TGF-beta), insulin-like growth factors I and II, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and bone morphogenetic protein (BMP), used alone or in combination with other biomaterials such as bioabsorbable polylactic acid, polyglycolic acid, collagen and calcium phosphates.
- Cell-based bone graft substitutes use cells to generate new tissue alone or are seeded onto a support matrix (e.g., mesenchymal stem cells seeded onto a porous collagen scaffold).
- Ceramic-based bone graft substitutes include calcium phosphate, calcium sulfate, and bioglass used alone or in combination. Approximately 60% of the bone graft substitutes currently available involve ceramics, either alone or in combination with another material.

- Polymer-based bone graft substitutes, degradable and nondegradable polymers, are used alone or in combination with other materials.

Consequently, the existence of numerous categories of bone graft substitutes, each encompassing a variety of materials, material sources, and origins, highlights the fact that the bone graft substitute genus includes a substantially large number of species.

22. I specifically performed a search on the "PubMed" database on or about December 4, 2008 using the keywords "Bone Graft Substitutes". A printout of the search results is attached as Exhibit B. As seen from this Exhibit B, the keywords "Bone Graft Substitutes" returned **1,902 citations**. Of these 1,902 citations, only 147 included the keywords "Demineralized Bone Matrix (DBM)". The bulk of the citations (i.e., **over 1700 citations**) were related to citations directed to **other** species of bone graft substitutes. Given such a large number of species available in the bone graft substitute genus, a person of ordinary skill in the art would not be motivated to specifically select the species of Demineralized Bone Matrix, over any of the other species encompassing the bone graft substitute genus.

23. The Jarrett et al. reference does not expressly teach a particular reason to select the specific species of Demineralized Bone Matrix, especially since there is no teaching or suggestion in Jarrett et al. of a composition comprising the Jarrett et al. carrier composition and a bone graft substitute material to promote the formation of new bone. Given no express teaching or particular reason as to why a person of ordinary skill in the art should select the specific species of Demineralized Bone Matrix, it is my opinion that a person of ordinary skill in the art would not have been motivated to choose the specific species of Demineralized Bone Matrix over any of the other species encompassing the bone graft substitute genus.

24. The Jarrett et al. reference also does not teach a "typical", "preferred," or "optimum" "incorporated agent, such as a prophylactic, therapeutic or diagnostic agent" to promote the formation of new bone. As described above, several categories of bone graft substitutes exist and encompass a variety of materials, material sources, and origins (natural vs synthetic). Many bone graft substitutes are formed from composites of 1 or more types of material. Considering the number of variables which must be selected or modified, and the nature and significance of the differences between the large number of bone graft substitute materials, it is my opinion that a person of ordinary skill in the art would not have been motivated to specifically choose the species Demineralized Bone Matrix over any of the other species encompassing the bone graft substitute genus.

25. Consequently, based on the above, it is my opinion that the specific selection of the species Demineralized Bone Matrix for the large genus of "bone graft substitutes" is hindsight. Even if a person of ordinary skill in the art would have been motivated to take a broad interpretation of the teachings of the Jarrett et

al. reference of "[i]n orthopedic surgery, uses include tendon repair, bone repair, including filling of defects, and meniscus repair" to include promoting the formation of new bone using a composition comprising an osteotherapeutic bone graft substitute material, which in no way is conceded to, the size of the prior art genus of "bone graft substitute" is so large that a person of ordinary skill in the art would not have been motivated to specifically select the species Demineralized Bone Matrix, over any of the other species of the bone graft substitute genus.

26. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Respectfully submitted,

Steve Lin

By: Dr. Steve T. Lin on January 22, 2010